

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Approach to Patients with SLE Presenting with Neurological Findings

Alkhotani Amal
Umm AlQura University
Saudi Arabia

1. Introduction

The nervous system is commonly involved by SLE. Its involvement classified as primary when it is related to the disease process and secondary when it is related to other factors like medication side effect or infection. The nervous system involvement by lupus was described by Hebra and Kaposi in 1875 who described a patient with lupus and coma (Appenzeller et al., 2006). Shortly after Bowen report case of psychosis and mood disturbance (Appenzeller et al., 2006).

The nervous system involvement rang from overt presentation to more subtle finding. In spite the advances in SLE diagnosis and managements, the neuropsychiatric syndromes remain one of the major causes of morbidity and mortality in SLE patients. Still they remain poorly understood and under recognised. The aim of this chapter is provide an overview of neurological presentation in SLE patients.

2. Definition

As there is wide Varity of different neurological and psychiatric presentations among SLE patient, the American college of Rheumatology (ACR) established in 1999 19 different neuropsychiatric SLE (NPSLE) syndromes (table-1). Either central or peripheral nervous system can be affected by the disease process. Their involvement can be generalized e.g headache, cognitive dysfunction or focal e.g. cerebrovascular disease and demyelinating syndromes.

Before attributing any of the neuropsychiatric (NP) manifestation to SLE secondary causes should be ruled out. As most of SLE patient are immunocompromised either by the disease process or secondary to immunocompressive therapy infection is a common problem in this patients. Other secondary causes can be metabolic impairments or complication from hypertension e.g posterior reversible leukoencephalopathy.

3. Epidemiology

The reported prevalence of NPSLE is varied from 37- 95 % (Muscal & Brey, 2010) depending on the case definition used and the inclusion criteria. Most of NPSLE affect central nervous system (91.6%) and out of those 79% are diffuse in nature and 21% focal (Hanly et al., 2008). The peripheral nervous system involvement is much less than CNS involvement.

NPSLE Associated with Central Nervous System	NPSL Associated with Peripheral Nervous System
<ul style="list-style-type: none">- Aseptic Meningitis- Cerebrovascular disease- Demyelinating syndromes- Headaches- Movement Disorders (Chorea)- Myelopathy- Seizure Disorders- Acute Confusional State- Anxiety Disorders- Cognitive Dysfunction- Mood Disorders- Psychosis	<ul style="list-style-type: none">- Acute Inflammatory Demyelinating Syndromes (Gulliaian –Barre Syndrome)- Autonomic Neuropathy- Mononeuropathy, single or multiplex- Myasthenia Gravis- Cranial Neuropathy- Plexopathy- Polyneuropathy

Table 1. Neuropsychiatric Syndromes Associated with SLE

The most frequently reported PNS involvement is peripheral neuropathy between 2.4to 7% (Hanly et al.,2010)(Ainiala et al.,2001). Recently Hanly and his colleague conducted a large cohort of SLE patients. They reported around 40.3% of SLE patient had at least one NP event and 17.4% had recurrent events (Hanly et al.,2010). The most frequent NP was headache 47.1% followed by mood disorders in 16.5%, Seizure in this cohort reported in 7.5% and cognitive dysfunction in 5.1%.

In other studies when a mild cognitive impairment and mild mood disorders were included higher prevalence of NPSLE is 80-91% (Ainiala et al.,2001)(Brey et al.,2002). When formal neuropsychiatric evaluation is used cognitive dysfunction is reported in 80% of the patient (Ainiala et al.,2001)(Brey et al.,2002). In 70% of those are classified as mild cognitive impairment with impairment of one or two cognitive domains (Ainiala et al.,2001).

The reported prevalence of cerebrovascular accident range between 4.7 to 15% (Hanly et al., 2010) (Ainiala et al.,2001).

The prevalence of other NPSLE syndromes is much less with reported prevalence of demyelinating syndrome and movement disorder of 1%.

CNS manifestations present as an initial feature of SLE in 24% of cases (Joseph et al.,2007). In general around 50-60% of NPSLE occurred at disease onset or within the first year after SLE onset.

3.1 Risk factors

Risk factors associated with CNS involvements are:-

1. Generalized disease activity.
2. Prior history or concurrent NPSLE.
3. Presence of antiphospholipid antibodies especially for focal CNS lesions and seizure (The European League Against Rheumatism EULAR, 2010).It was also noted that patients with APS who had a history of two or more abortion are six times more likely to have CNS events(Karassa et al.,2000).

In term of SLE disease activity two studies have shown that skin lesions are the most frequent lesions associated with CNS disease (EULAR, 2010)(Karassa et al.,2000). Two

studies have shown a protective effect of arthritis to CNS disease ((EULAR, 2010). This was not consistent in other study where arthritis was a second common manifestation after skin disease (Joseph et al.,2007).

4. Pathogenesis

The neuropsychiatric lupus has different manifestations. As the manifestations can be generalized or focal no single pathophysiological mechanism has been implicated in its pathogenesis. Different mechanisms are thought to affect the nervous system and caused the development of NPSLE. Those different mechanisms include vasculopathy, autoantibodies and cytokines.

4.1 Vasculopathy

Vascular occlusion is universally reported in autopsy cases in patient with lupus. Although vasculitis is thought to be the cause of small vessels disease in lupus patient, its occurrence is rare. The most frequent cause is found to be a non inflammatory vasculopathy.

On pathology multiple microinfarcts, cortical atrophy, gross infarcts were seen on the brain. Microhemorrhages are common in NPSLE. Larger haemorrhages like intracerebral are rare. The most common vascular pathology is noninflammatory lesions characterized by endothelial proliferation, intimal fibrosis and lymphocytic infiltration. It may associated by thrombosis (Ellison et al.,1993).

The pathogenesis of the vascular injury initially thought to be secondary to immune complex deposition but now it thought to be secondary to complement activation (Muscal & Brey, 2010).

4.2 Autoantibodies

Autoantibodies play a major role for the development of different manifestations of SLE. Different antibodies have been reported in association with NPSLE. Among those the most frequent antibodies are antiphospholipid (API) and antiribosomal abs.

Antiphospholipid antibodies that includes lupus anticoagulant, anti cardiolipin and anti-beta2 glycoprotein I antibodies are groups of antibodies which target the phospholipid binding plasma proteins such as beta 2 glycoprotein I and prothrombin. As they alter the expression and secretion of procoagulant on the cell surface they subsequently prompt thrombosis.

Their presences were associated with recurrent thrombosis and fatal losses. Multiple neurological presentations are linked to their presence in patient with and without SLE. It associated in particular with focal neurological events like stroke. They also have linked to seizure, movement disorders, cognitive impairment and myelitis.

A subset of anti- DNA antibodies were found to react with NR2 glutamate receptors. Glutamate is an excitatory neurotransmitter in the brain. It react with NMDA(N-methyl-D-aspartate) receptors which is present throughout the brain tissue. NMDARS that containing NR2A and NR2B are more expressed in CA1 region of the hippocampus and the amygdale. Excessive stimulation of NMDARS results into excessive influx of calcium into the neuronal tissue causing mitochondrial stress and subsequent neuronal death (Aranow et al, 2010).

In animal models anti NR2 receptors antibodies did not cause brain damage in the presence of intact blood brain barrier (BBB). When BBB compromised using bacterial

lipopolysaccharide (LPS) damage to hippocampal neurons took place with no evidence of inflammation. Those mice performed badly on memory function (Kowal et al,2004). When epinephrine is used to compromise the BBB the hippocampus of those mice was normal but the antibodies react with neurons of the amygdale. Those mice had impaired fear response (Huerta et al.,2006).

Studies have shown a correlation between the CSF anti- NR2 level with diffuse NPSLE not with focal NPSLE (Arinuma et al, 2008) and no relation to serum anti-NR2 level. This may implicate intrathecal production of anti-NR2 antibodies or migration of antibodies through compromised BBB.

Anti- ribosomal P antibodies was reported in association with SLE. Their presence was linked to lupus related Psychosis and depression.

4.3 Cytokine effects

Elevated level of interleukin (IL-1),IL2, IL-6, IL-8, and interferon gamma (IFN γ) were found in the CSF of patient with NPSLE (Rhiannon, 2007)(Chandy et al.,2008). Also elevated level of tumour necrosis factor (TNF) family ligands BAFF (B- cell activating factor of TNF family) and APRIL (a proliferation- inducing ligand) were seen in CSF of SLE patients. However the level of APRIL was higher in NPSLE patients when compared to SLE patient without NP (Chandy et al,2008).

The cytokines are thought to be produced locally by the infiltrating immune cells or by the glial cells or the neurons. Different cytokines had different effects. Their role in the pathogenesis of NPSLE is related to stimulating antibodies productions, effecting neurotransmitter release and the release of corticotrophin releasing hormone (CRH). The stimulation of glucocorticoid production results in persistent elevation of glucocorticoid that plays a role in hippocampal atrophy.

5. Approach

A careful evaluation of SLE patients presenting with new neurological symptoms and signs is needed to rule out secondary causes before attributing it to SLE. Different secondary causes can be a cause for neurological symptoms in SLE patients. The management will be different if the presentation related to lupus or to other causes.

The evaluation of SLE patients presenting with neurological symptoms and signs will be the same as non SLE patients. This includes careful clinical, laboratory and imaging studies. The diagnosis of NPSLE is a diagnosis by exclusion. No single laboratory or imaging study will confirm that the neurological presentation is caused by SLE itself. The presence of other lupus related activity could support the diagnosis of NPSLE.

5.1 History

Detailed history is mandatory when evaluating lupus patient presenting with new neurological presentation. Detailed description of the neurological symptoms is necessary to assist for localization and identifying a potential cause for the problem. The onset of the symptoms will help identifying problems with acute versus more chronic disorder. The severity of the presentation and associated other neurological symptoms will help in determine the nature and will assist further regarding the management plan. The presence of fever may suggest the presence of infection.

Detailed SLE history regarding time of diagnosis, disease course, previous neurological presentation and complications related to disease are particularly important. Most of NPSLE present at time of generalized disease activity. Patients with prior neurological involvement are also at higher risk to have recurrence or development of other neurological disorders. Neurological complications can be also developed secondary to other organ involvement by lupus for example acute stroke can be a presentation of Libman Sacks endocarditis, or in other example patient may develop posterior reversible leukoencephalopathy (PRES) secondary to hypertension which can be secondary to renal disease in lupus patient. Detailed drug history is important as patient may develop complication related to therapy like psychosis from steroid therapy. Patient on immunosuppressive treatment are immunocompromised so they are at high risk of development of bacterial, viral and fungal infections. Subacute neurological symptom in SLE patient may represent JC virus infection that causes progressive multifocal leukoencephalopathy (PML). PML is a demyelinating disease that mainly reported with HIV patients. Multiple cases of PML also reported in SLE patient either on or not on immunosuppressive therapy (Molloy & Calbrese, 2009). The possibility of infection should be ruled out before attributing a neurological presentation to SLE and starting aggressive immunosuppressive therapy.

Other medication history might be the cause for the neurological presentation. In particular antipsychotic therapy as they can induce movement disorders. The management in that instance will necessitate medication changes rather than immunosuppression.

Detailed family history of same problem or other neurological disorders may point to genetically related neurological diagnosis not necessarily attributing it to SLE.

When patient presents acutely with symptoms and signs suggestive of acute stroke a quick assessment is necessary not to delay thrombolytic therapy if indicated (further discussion regarding cerebrovascular disease is discussed below).

In patient presenting with seizure careful history to characterize the seizure whether it is generalized or focal. The presence of focal seizure could represent structural lesion as a cause of the seizure. Careful medication and systemic review is mandatory as the seizure can be secondary to metabolic abnormalities e.g. uremia or medication induced seizure. The presence of other associated neurological symptoms could point to other possible causes of seizure. In particular the presence of headache, disturbed conscious level could be related to posterior reversible leukoencephalopathy, limbic encephalitis or viral encephalitis. The presence of other focal neurological deficit can point to structural lesions such as stroke. One should exclude other non lupus related causes of seizure such as head trauma or genetically determined epilepsy.

5.2 Examination

The aim of the examination is to localize the neurological presentation and reach a possible diagnosis which will be supported by the laboratory investigations.

Careful systemic as well neurological examinations are required when dealing with SLE patients with neurological presentation. In particular patient needs to be checked for fever, and had blood pressure measurements. The presence of other areas of vascular occlusion could point to vascular cause of the neurological events.

In patient presenting with cognitive problem full neuropsychological assessment should be carried out. That will include assessing simple attention, complex attention, memory, visuospatial processing, language, reasoning/problem solving, psychomotor speed and executive functions.

5.3 Laboratory examination

Full laboratory assessment to rule out infection and metabolic abnormality that could be the cause for the neurological events. That will include complete blood count, electrolytes, kidney and liver function test. Cerebrospinal fluid assessment is necessary in certain cases to rule out infection or other unrelated condition. In patient with subacute presentation and demylination on imaging the CSF should be sent for JC virus PCR. The CSF level of autoantibodies and inflammatory mediators are not recommended now as it still a research interest.

5.4 Supplementary tests

EEG is indicated in patient presenting with seizure or in patient with acute confusional state. For patient with seizure the EEG will help in determine the subset of patients who are at high risk of seizure recurrence. The most frequent EEG abnormalities reported in SLE patient is bitemporal slowing in 65% of patients (Lampropoulos et al., 2005). Nerve conduction study and electromyography is indicated in patient presenting with peripheral nervous system related complaints.

5.5 Imaging

In acute setting in patient presenting with acute onset neurological events computerized tomography (CT) brain is the imaging modality of choice to rule out haemorrhage. It is also an easily accessible and widely available. The use of CT brain initially will be important to identify a subset of patients who may need thrombolytic therapy. MRI (magnetic resonance imaging)is a preferred imaging modality to evaluate lupus patients with neurological symptoms. It is more sensitive than CT in detecting anatomical abnormalities and determines the extent of disease process. The most frequent abnormalities in MRI is hyperintense white matter lesions which is seen in 70% of patients (Appenzeller et al.,2007).Their presence have been linked to the presence of Apl . Cerebral atrophy is seen in 6-12% in SLE patients (Huizinga et al.,2001)(Appenzeller et al.,2005-2007). Other advanced imaging technique may be of value in assessing patients with NPSLE although there clinical uses are not widely available. Those includes MTR (magnetization transfer ratio), diffusion weighted images, MRS (magnetic resonance spectroscopy), functional MRI and single photon emission computed tomography.

Investigation	
Laboratory	CBC, Electrolytes, Kidney and liver function
CSF	WBC, Glucose, protein, Gram stain and culture Viral PCR
Imaging	CT brain MRI brain and spinal cord
Electrophysiology	EEG EMG

CBC, complete blood count; WBC, white blood cell; CT computerized tomography; MRI , magnetic resonance imaging; EEG, electroencephalogram

Table 2. Recommended investigation in SLE patient with neurological presentation

6. Management

Once the diagnosis of NPSLE is confirmed the treatment will include treatment of potential aggravating factors, symptomatic treatment for the events and more specific treatment related to SLE itself.

In some condition symptomatic treatment will be required first before specific therapy is indicated. For example in patient presenting with seizure after excluding secondary causes starting antiepileptic is required before the decision on specific treatment is made (Hanly & Harrison, 2005).

The severity and the nature of neurological events will also play a role in the decision on treatment. For example patient with non serious headache will require only symptomatic treatment.

In the presence of severe neurological disease the European League Against Rheumatism (EULAR, 2010) recommends the use corticosteroid alone or with cyclophosphamide. A Cochrane review of cyclophosphamid versus methylprednisolone in treatment of NPSLE did not find a randomised clinical trial comparing the two.

When patient failed to respond to conventional treatment or in the presence of severe disease multiple reports suggested the addition of other treatment modalities can be effective. Those include plasma exchange, rituximab or intravenous immunoglobulin.

The combination of the treatment modalities (cyclophosmaide/corticosteroid/ plasma exchange (Bartolucci et al., 2007) or plasmapheresis alone or with cyclophosphamide (Neuwelt, 2003)) was evaluated in small series of refractory disease. Results from those showed favourable outcome with combination modalities.

Rituximab is an anti-CD20 antibody that directly target B cells. Rituximab was studied in refractory cases of NPSLE and showed a rapid improvement of clinical as well radiological finding in those patients (Takunaga et al., 2006).

In the presence of thrombotic disease the management will depend whether patient had arterial versus venous thrombosis and the presence of antiphospholipid. Anticoagulation is recommended for venous thrombosis as well in the presence of arterial thrombosis with antiphospholipid antibodies. In absence of antiphospholipid antibodies and the presence of arterial thrombosis careful evaluation and management for secondary risk factors with the use of antiplatelets are indicated.

7. Common neurological disorders associated with SLE

7.1 Headache

Headache is one of the most commonly reported neurological symptoms associated with SLE. There is no specific type of headache found to have increase prevalence in patient with SLE (Mitsikostas, 2004).

When patient with SLE patient present with acute headache, special attention is warranted to rule out infection, aseptic meningitis and venous sinus thrombosis. On examination special attention is required looking for fever, meningeal signs and examination for the fundi to rule papilledema. In the presence for focal finding, papilldema or altered mental status brain imaging is required. Brain MRI with venogram is preferred to rule out venous sinus thrombosis. In presence of fever or signs of infection CSF examination is mandatory.

No specific treatment is required for nonspecific headache.

7.2 Cognitive dysfunction

It is one of the most commonly reported NPSLE syndromes. Most of the patient had mild to moderate impairment, only around 3-5% had severe impairment (EULAR, 2010). The most commonly reported abnormality is overall slowing, decrease memory, impaired working memory and executive dysfunction (Hanly, 2005).

Different report linked cognitive impairment to the presence of APL (McLurin et al., 2005) (Denburg et al., 1997). It is also reported in patient who suffered from stroke and with APL microinfarcts although the pattern is different between the two. Cognitive dysfunction from stroke develops acutely and remains the same in contrast to those with microinfarct as it shows stepwise deterioration. Different studies have showed a contradicting results regarding the association between global disease activity and the presence of cognitive impairment (Kozora et al., 1996) (Hay et al., 1992) (Carbotte et al., 1995). Some of the studies found an association and other did not find any association. The use of glucocorticoid associated with cognitive impairment in middle age patients irrespective of disease activity (McLurin et al., 2005). The effect of prednisone use was not significant for young and old patients.

Other causes can alter the cognitive function. Of those the development of mood disorders are particularly important. It is very well known that depression worsen cognitive function and even cause a pseudodementia. Patients with SLE also under psychological stress from the disease itself or from medications and that also can alter cognitive function even in absence of psychiatric disease (Hanly, 2005).

Formal neuropsychological testing is required to diagnose cognitive dysfunction. The main limitation of formal neuropsychological testing is time consuming and it need to be administered by an expert. The minimal test is not a good tool for screening for cognitive impairment.

MRI is indicated if the patient is less than 60 years, rapid and unexplained moderate to severe impairment, recent and significant head trauma, presence of other neurological symptoms or signs and the development of it in the setting of immunosuppressive therapy or antiplatelets (EULAR, 2010).

Patient should be screened and treated for potential precipitating factors such as metabolic and endocrine abnormalities. Associated psychiatric disorders should be treated. Control of cardiovascular risk factors also is recommended. McLaurine in 2005 reported a beneficial effect of regular aspirin use on cognitive function in elderly patient with other vascular risk factors particularly in diabetics (McLurin et al., 2005).

The use of glucocorticoid with or without immunosuppressive will be considered in the presence of SLE disease activity or other NPSLE events.

Memantine is a drug used to treat dementia. One randomized clinical trial looked at the use of memantine to treat patient with SLE and cognitive impairment. No significant improvement in cognitive function in the treated group. At current the use of memantine for SLE patient with cognitive impairment is not recommended. Further clinical trial is needed (Petri et al., 2011).

7.3 Cerebrovascular disease

SLE patients are at high risk of developing vascular complications. Among those are stroke and transient ischemic attacks. Multiple causes can lead to strokes in SLE patients. The most frequent cause is atherosclerotic diseases. Other rare causes include embolic strokes from Libman-Sacks endocarditis and cerebral vasculitis.

In study of carotid ultrasound in asymptomatic SLE patients carotid plaques were seen in 25-40% of patients. Different risk factors were associated with the development of strokes in SLE patients. Those includes high disease activity, moderate to high titres of antiphospholipid antibodies, heart valve disease, hypertension, age and smoking (EULAR, 2010) (Tolosa et al,2004)(Bessant et al.,2004)(Futrell & Millikan,1988).

Evaluation of stroke/TIA patient will be the same as non SLE patient. Thrombolytic therapy can be given unless there are contraindications. Patient should be screened for cardiovascular risk factors and have aggressive measures to control them. Further managements will include the use of antiplatelet and carotid endarterectomy if indicated. Patients who fill full the criteria of antiphospholipid syndromes chronic anticoagulant therapy is indicated with a target INR of 2-3 (EULAR,2010)(Crowther et al,2003)(Finazzi et al.,2005).

7.4 Seizure

Seizure in SLE patient can be attributed to the disease activity or it could be related to secondary causes. The secondary causes of seizure in SLE patients are:- infection, electrolytes abnormalities, uremia, hypertension, medication side effect or hypoxia. It also can be a presentation of unrelated condition such as brain tumours.

The reported prevalence of seizure is between 7.5% to 14% (Hanly et al.,2010)(Mikdashi et al.,2005)(Appenzeller et al.,2004). Seizure present at disease onset in 31.7% of patients (Mucal & Brey,2010), and most frequently occurred within 5 years from diagnosis. Most of the patient 88.3% had single events and around 11.7% had epilepsy. The most frequently reported seizure type is generalized tonic clonic seizure followed by complex partial seizure. Seizure can present as the only NP syndrome or accompany other neurological events mainly ischemic or hemorrhagic strokes and psychosis.

Multiple studies confirmed the relation between seizure and the presence of APL(Mikdashi et al.,2005)(Appenzeller et al.,2004)(Gibbs & Husain,2002)(Herranza et al.,1994)(Liou et al.,1996). Also the presence of APL were associated with shorter time to seizure occurrence (Andrade et al.,2008). Seizure occurrence is related to high disease activity, severe organ damage in particular nephritis and the presence of APL. Factors associated with epilepsy are the same as those associated with seizure. Patients who had epilepsy are more likely to be men (Mikdashi et al.,2005) and more likely to have abnormal MRI and EEG.

The most frequent abnormality reported in brain MRI in patient with seizure is global atrophy and the presence of multiple subcortical hyperintense lesions. The most frequent EEG finding is diffuse slowing. The presence of interictal epileptic activity is associated with high recurrence rate of epileptic seizure.

As most of the patients will have only one seizure, treatment with antiepileptic is not recommended. The patient should be investigated with EEG, brain MRI and have APL antibody screening. Patient who had positive test for APL should be monitored carefully as they have high recurrence rate. In the presence of other SLE activity or flare treatment with glucocorticoid with or without immunosuppressive is recommended (EULAR, 2010).

7.5 Acute confusional state

It is a condition characterized by acute onset of altered mental state with decrease attention. A careful exclusion of secondary causes such as metabolic, infection and side effect of medications is mandatory. CSF examination is required to exclude infection. Brain imaging is indicated to rule out structural lesions. EEG is also indicated to rule out seizure disorders.

Treatment includes symptomatic treatment with antipsychotics to control agitation, glucocorticoid and immunosuppressive agents.

7.6 Myelopathy

Patient with SLE may present with symptoms and signs of spinal cord dysfunction which may indicate the presence of myelitis. Myelitis is less commonly reported than other NPSLE syndromes (1-3% of patient) (Lukjanowicz & Brzosko, 2009). Most commonly patient will present with acute transverse myelitis and less commonly will have longitudinal myelitis.

Acute transverse myelitis involves less than 4 segments of the spinal cord in contrast to longitudinal myelitis which involve more than 4 segments of the cord. The thoracic cord is the most commonly affected followed by the cervical cord (D'Cruz et al., 2004).

Around 73% of SLE patient presenting with myelitis were positive for aPL (D'Cruz et al., 2004).

Patient with myelitis present acutely with motor weakness and sensory symptoms. The extent of the symptoms depends on the level of the lesion and the extent of the inflammatory changes. Bladder and bowel dysfunction is seen in all patients with myelitis.

Lupus myelitis is usually developed in the first 5 years after disease onset (Kovacs et al., 2000) (Chan & Boey, 1996). One third of the cases have another major NPSLE (EULAR, 2010). In 21-48% of patients will have associated optic neuritis (Kovacs et al., 2000) (Chan & Boey, 1996). The recurrence rate for myelitis is seen in 21-55% of patients (Kovacs et al., 2000) (Chan & Boey, 1996) (Lehnhardt et al., 2006).

When patient with SLE present with feature of myelopathy a careful exclusion of other causes of myelopathy is necessary before attributing the presentation to SLE. A contrast enhanced MRI of spinal cord is mandatory to rule out mass lesions as a cause for myelopathy. The most frequently reported abnormalities are T2 hyperintensities which become more pronounced after contrast (Lukjanowicz & Brzosko, 2009) (Provenzale et al., 1994) (Boumpas et al., 1990) (Salmaggi et al., 1994). In a group of patients the initial MRI can be normal especially if it was done early. If the initial MRI is normal repeat study in 2-7 days after onset is recommended (Lukjanowicz & Brzosko, 2009). Brain MRI is indicated when there is associated neurological symptoms and to help differentiating it from multiple sclerosis.

Cerebrospinal fluid examination is recommended to rule out infectious aetiology (EULAR, 2010). In 50-70% of cases mild CSF abnormalities are seen including mild lymphocytosis and elevated protein with normal glucose.

An inflammatory CSF with granulocytes pleocytosis, elevated protein and low glucose is reported with lupus myelitis especially with longitudinal myelitis. In the presence of this finding a careful exclusion of infectious cause is mandatory.

In the presence of longitudinal myelitis and associated optic neuritis serum should be sent for anti neuromyelitis antibodies (anti-NMO IgG) to rule out the presence of neuromyelitis optica. Anti NMO IgG is a highly sensitive and specific antibody that targets aquaporin 4 the main water channel in the CNS.

An aggressive treatment with immunosuppressive is recommended in a setting of ATM. The presence of inflammatory CSF should not delay the start of immunosuppressive. In that case a combined treatment of antimicrobial with immunosuppressive is recommended waiting for the culture results. Antimicrobial should be discontinued once infection is ruled out.

Treatment with intravenous steroid should be initiated followed by cyclophosphamide with oral steroid.

The treatment should be initiated early in the disease course.

Plasmapheresis has been used with immunosuppressive medication in severe cases in particular in patient with longitudinal myelitis ((D'Cruz et al.,2004). Although an earlier reports by Kovacs showed patients who had combined treatment of steroid, immunosuppressive and plasmapheresis did worse than patient who had only steroid with or without immunosuppressive (Kovacs et al.,2000). This is may be because patients who had aggressive treatments with three modalities had higher disease activity at the onset of myelitis.

In the presence of Apl anticoagulant therapy is recommended with the immunosuppressive therapy. Patients with apl and Transverse myelitis who had combination therapy of immunosuppressive and anticoagulant have good functional outcome (D'Cruz et al.,2004).

The functional outcome is good for patient who had early treatment. The presence of longitudinal transverse myelitis is associated with poor functional prognosis (Gertner,2007)(Kimura et al.,2002).

7.7 Movement's disorders

The most frequently reported movement disorder with SLE patient is chorea. It has been linked to antiphospholipid antibodies. Other causes of chorea such as hereditary, metabolic, endocrine causes should be excluded. Brain imaging is indicated to rule out structural causes in the presence of focal neurological signs.

Patient need to be treated symptomatically with dopamine antagonist and in severe cases the use of glucocorticoid and immunosuppressive therapy is recommended. In the presence of antiphospholipid antibodies patient need to be on antiplatelets or anticoagulants depending on the presence of other APS related symptoms.

Parkinsonism is also reported in association with SLE in multiple cases. Usually it is associated with severe multisystem CNS involvements. The good response of the reported cases to immunosuppressive therapy suggests that it is a manifestation of the disease not a coincidence of Parkinson disease and SLE.

7.8 Peripheral nervous system Involvements

Peripheral neuropathy is the most frequent reported peripheral nervous system (PNS) involvement with SLE. The most frequent type is sensory neuropathy followed by sensorimotor neuropathy then pure motor neuropathy (Goransson et al.,2006).A subset of SLE patients may present with sensory symptoms and still have normal NCS. This is because the NCS evaluate the large myelinated fibers and the presence of normal study does not rule out small fiber neuropathy. In studies when symptomatic patients with negative NCS had skin biopsy an evidence of small fiber neuropathy was found (Goransson et al.,2006)(Omdal et al.,2002). This indicates that small fiber neuropathy is the cause of the symptomatic patients with normal NCS. Managements of peripheral neuropathy include symptomatic treatments for neuropathic pain as well glucocorticoid with or without immunosuppressive therapy depending on the severity of the disease. In the presence of severe cases, or failure of conventional treatments other modalities such as plasmapheresis, intravenous immunoglobulin and rituximab can be used.

Other PNS involvements by SLE are much less. Patient may present with mononeuritis multiplex, acute demyelinating polyradiculopathy, chronic demyelinating polyradiculopathy

and myasthenia gravis also reported. The managements of those patients will be the same as non SLE patients.

8. Prognosis

In spite of recent advances in diagnosis and management, NPSLE remain one of the major causes of disease related morbidity. Swedish study of SLE patients did not find difference in mortality in SLE patients with or without NP. However patients with NPSLE have more functional impairments when compared to non NPSLE patients (Jonsen, 2002). Prompt diagnosis and management may played a role in reducing mortality but significant morbidity and functional incapacity still a major problem in SLE patients with neuropsychiatric symptoms.

9. Acknowledgment

The work to produce this chapter was supported by Alzaidi's Chair of research in rheumatic diseases- Umm Alqura University.

10. References

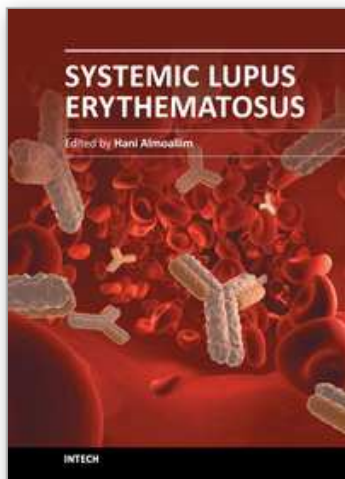
- H.Ainiala, J. Lukkola, J.Peltola, et al. The Prevalence of Neuropsychiatric Syndromes in Systemic Lupus Erythematosus. *Neurology* 2001;57: 496-500.
- Andrade, Alarcon, et al. Seizure in Patients with Systemic Lupus Erythematosus: data from LUMINA, a multiethnic Cohort. *Ann Rheum Dis* 2008;67(6):829-834
- Antonella, Garzia, et al. Neuropsychiatric Lupus Syndromes: Relationship With Antiphospholipid Antibodies. *Neurology* 2003;61:108-110.
- Appenzeller, Cendes, Costallat. Epileptic Seizure in Systemic Lupus Erythematosus. *Neurology* 2004;63:1808-1812
- Appenzeller, Bonilha, et al. Longitudinal Analysis of Gray and white Matter Loss in Patients with Systemic Lupus Erythematosus. *Neuroimage* 34;694-701.
- Appenzeller, Rondina, Costallat, Cendes. Cerebral and Corpus Callosum Atrophy in Systemic Lupus Erythematosus. *Arthritis Rheum* 2005; 52: 2783-2789.
- Appenzeller, Costallat, Cendes. Neurolupus. *Arch Neur* 2006;63:458-460. Appenzeller, Pike, Clarke. Magnetic Resonance Imaging in the Evaluation of Central Nervous System Manifestation in Systemic Lupus Erythematosus. *Clin Rev Allerg immunol* 2007.
- Aranow, Diamond, Mackey. Glutamate Receptor Biology and its Clinical Significance in Neuropsychiatric SLE. *Rheum Dis Clin North Am.* 2010 February;36(1):187-201
- Arinun et al. Association of Cerebrospinal Fluid Anti-NR2 Glutamate Receptor Antibodies with Diffuse Neuropsychiatric Systemic Lupus Erythematosus. *Arthritis and Rheumatism.* 2008 April;58(4):1130-1135.
- Barile-fabris, et al. Controlled Clinical Trial Of IV Cyclophosphamide versus IV Methylprednisolone in Severe Neurological Manifestation in Systemic Lupus Erythematosus. *Ann Rheum Dis* 2005;64:620-625.
- Bartolucci, Brechignac, et al. Adjunctive Plasma Exchange to Treat Neuropsychiatric Lupus: a Retrospective Study on 10 Patients. *Lupus* 2007;16(10):871-822.

- Bertsias et al, EULAR recommendations for the management of Systemic Lupus Erythematosus with neuropsychiatric manifestation: report of task force of the EULAR standing committee for clinical affairs. *Ann Rheum Dis*, 2010; 69: 2074-2082
- Bosma, Huizinga, et al. Abnormal Brain Diffusivity in Patient with Neuropsychiatric Systemic Lupus Erythematosus. *AJNR* 2003; 24:850-854.
- Bosma, Steens, et al. Multisequence magnetic Resonance Imaging Study of Neuropsychiatric Systemic Lupus Erythematosus. *Arthritis & Rheumatism* 2004; 50(10):3195-3201
- Boumpass, et al. Acute Transverse Myelitis in Systemic Lupus Erythematosus: magnetic Resonance Imaging and review of Literature. *J Rheumatol* 1990;17:89-92.
- Brey, Holliday, et al. Neuropsychiatric Syndromes in Lupus. *Neurology* 2002;58:1214-1220
- Brey. Neuropsychiatric Lupus Clinical and Imaging Aspects. *Bulletin of the NYU Hospital for Joint Diseases* 2007;65(30):194-199.
- Briani, Lucchetta, et al. Neurolupus is Associated with Anti-ribosomal P protein Antibodies; an Inception Cohort Study. *J Autoimmun* 2009 Mar; 32(2):79-84.
- Carbott, Denburg. Cognitive Dysfunction in Systemic Lupus Erythematosus is independent of active disease. *Journal of Rheumatology* 1995;22:863-867.
- Castellino, Padovan, et al. Single Photon Emission Computed Tomography and Magnetic Resonance Imaging Evaluation in SLE Patients with and without Neuropsychiatric Involvement. *Rheumatology* 2008; 4:319-323.
- Chan, Boey. Transverse myelopathy in SLE: clinical and Functional outcomes. *Lupus* 1996;5:294-299.
- Chandy, Trysberg, Eriksson. Intrathecal Levels of APRIL and BAFF in Patients with Systemic Lupus Erythematosus: relationship to Neuropsychiatric Syndromes. *Arthritis Research & Therapy* 2008;10 (4).
- Crowther, et al. A Comparison of two intensities of Warfarin for the Prevention of Recurrent Thrombosis in Patient with Antiphospholipid Antibodies Syndromes. *N Eng J Med* 2003;349:1133-1138.
- D'Cruz, Mellor-Pita, et al. Transverse Myelitis as the First Manifestation Systemic Lupus Erythematosus or Lupus Like Disaas: Good Functional Outcome and relevance of Antiphospholipid Antibodies. *The J of Rheumatology* 2004;31:280-285.
- Denburg, Carbotte, et al. The Relationship of Antiphospholipid Antibodies to Cognitive Function in Patients with Systemic Lupus Erythematosus. *J int neuropsychol soc* 1997;3(4):377-386.
- Ellison, Gatter, Heryet, Esiri. Intramural Platelet Deposition in Cerebral Vasculopathy of Systemic Lupus Erythematosus. *J Clin Pathol* 1993; 46:37-40
- Eyal Muscal, Brey. Neurological Manifestation Of Systemic upus Erythematosus in Children and adult. *Neurol Clin*. 2010 Feb; 28(1);61-73
- Fady Joseph, Lammie, Scolding. CNS Lupus A study of 41 Patients. *Neurology* 2007; 69:644-654.
- Finazzi, et al. A Randomized Clinical Trial of High Intensity Warfarin vs Conventional Antithrombotic Therapy for the Prevention of recurrent Thrombosis in Patient with Antiphospholipid Syndrome. *J Throm Haemost* 2005;3:848-853.

- Furtrell, Millikan. Frequency , Etiology, and Prevention of Stroke in Patients with Systemic Lupus Erythematosus. *Stroke* 1989;20(5):583-590.
- Gibbis & Husain. Epilepsy Associated with Lupus Anticoagulant. *Seizure* 2002;11(3):207-209
- Goransson, et al. Small Diameter Nerve Fiber Neuropathy in Systemic Lupus Erythematosus. *Arch neurol* 2006;63:401-404.
- Hammad, Tsukada, Torre. Cerebral Occlusive Vasculopathy in Systemic Lupus Erythematosus and speculation on the part palyed by complement. *Annals of the Rheumatic Diseases* 1992;51:550-552
- Hanly, Harrison. Management of Neuropsychiatric Lupus. *Best Practice 7 Research Clinical Rheumatology* 2005;19(5):799-821).
- Hanly, Urowitz, Siannis, et al. Autoantibodies and Neuropsychiatric Events at the Time of Systemic upus Erythematosus Diagnosis. *Arthritis & Rheumatism*. March 2008 (58): 843-853.
- Hanly, urowitz, L. Su et al. Prospective Analysis of neuropsychiatric Events In An International Disease Inception Cohort of SLE Patients. *ann Rheum Dis*. 2010 March; 69(3): 529-535.
- Hay, et al. Psychiatric disorder and cognitive Impairment in Systemic Lupus Erythematosus. *Arthritis and Rheumatism* 1992;35(4):411-416.
- Heinlein, Gertner. Marked Inflammation in Catastrophic Longitudinal Myelitis Associated With Systemic Lupus Erythematosus. *Lupus* 2007;16:823-826.
- Herranz, Rivier, et al. Association between Antiphospholipid Antibodies and Epilepsy in Patients with Systemic Lupus Erythematosus. *Arthritis Rheum* 1994;37(4):568-571
- Hingorani, MacGregor, Isenberg, A. Rahman. Risk of Coronary Heart Disease and Stroke in a Large British Cohort Of Patients with Systemic Lupus Erythematosus. *Rheumatology* 2004;43:924-929.
- Huerta, et al. Immunity and Behavior, antibody alter emotion. *Proc Natl Acad Sci USA* 2006;103(3):678-683.
- Huizinga, Steens, Van Buchem. Imaging Modalities in Central Nervous System Systemic Lupus Erythematosus. *Curr Opin Rheumatol* 13:383-388.
- Jonsen, Bengtsson, et al. Outcome of Neuropsychiatric Systemic Lupus Erythematosus within a defined Swedish Population :increased Morbidity but Low Mortality. *Rheumatology* 2002;41:1308-1312
- Kato, et al. Systemic Lupus Erythematosus Related Transverse myelitis Presenting Longitudinal Involvement of The Spinal Cord. *Internal Medicine* 2002;41(2):156-160.
- Katsumata, Harigai, et al. Diagnostic Reliability of Magnetic Resonance Imaging for Central Nervous System Syndromes in Systemic Lupus Erythematosus: a prospective Cohort study. *BMC Musculoskeletal Disorders* 2010;11.
- Kovacs, Lafferty, et al. Transverse myelopathy in Systemic Lupus Erythematosus; an analysis of 14 cases and Review of the literature. *Ann rheuma dis* 2000;59:120-124
- Kowal, et al. Cognition and Immunity, antibody impairs memory. *Immunity* 2004; 21(2):179-188

- Kozora, et al. Analysis of Cognitive and Psychological Defecits in Systemic Lupus Erythematosus patients without overt Central Nervous System Disease. *Arthritis and Rheumatism* 1996;39(12):2035-2045
- Lampropoulos, Koutroumandis, et al. Electroencephalography in The assessment of Neuropsychiatric Manifestations in Antiphospholipid Syndrome and Systemic Lupus Erythematosus. *Arthritis & rheumatism* 2005; 52(3):841-846
- Lehnhardt,et al.Autologous Blood stem Cell Transplantation in refractory Systemic Lupus Erythematosus with Recurrent Longitudinal Myelitis and Cerbral Infraction. *Lupus* 2006;15:240-243.
- Levy, Uziel, et al. Intravenous immunoglobulins in Peripheral Neuropathy associated with vasculitis. *Ann Rheum Dis* 2003;62:1221-1223.
- Liou, Wang, et al. Elevated Levels of Anticardiolipin Antibodies and Epilepsy in Lupus Patients. *Lupus* 1996;5(4):307-312.
- Lukjanowicz, Brzosko. Myelitis in The Course of Systemic Lupus Erythematosus. *POI Arch MedWewn*2009;119:67-73.
- McLaurin, Holliday, Williams, Brey. Predictors of Cognitive Dysfunction in Patients with Systemic Lupus Erythematosus. *Neurology* 2005;64:297-303.
- Mikadashi, Krumholz,Handwerker. Factors at Diagnosis Predict Subsequent Occurrence of Seizure in Systemic Lupus Erythematosus. *Neurology* 2005;64:2102-2107.
- Mitsikostas, Sfikakis, Goadsby. A meta analysis for Headache in Systemic Lupus Erythematosus: the Evidence and the Myth. *Brain* 2004;127:1200-1209.
- Molloy, Calbrese. Progressive Multifocal Leukoencephalopathy. *Arthritis & Rheumatism* 2009;60(12):3761-3765
- Nasir, Kerr, Birnbaum. Nineteen Episodes of Recurrent Myelitis in a Woman With Neuromyelitis Optica and Systemic Lupus Erythematosus. *Arch neurol* 2009; 66(90):1160-1163.
- Neuwelt. The Role of Plasmapheresis in the Treatment of Severe Central Nervous System Neuropsychiatric Systemic Lupus Erythematosus. *Ther Apher Dial* 2003;7(20):173-182.
- Okamoto, kobayashi, Yamanaka. Cytokines and Chemokines in neuropsychiatric Syndromes of Systemic Lupus Erythematosus. *J of biomedicine and biotechnology* 2010.
- Okuma, et al. Comparison between Single antiplatelet therapy and Combination of Antiplatelet and Anticoagulation Therapy for Secondary Prevention in Ischemic Stroke Patients with Antiphospholipid Syndrome. *Int J Med Sci* 2010;7:15-18
- Omdal, et al. Peripheral Neuropathy in Systemic Lupus Erythematosus. *Neurology* 1991;41:808-811.
- Omdal, et al. Small Nerve Fiber Involvement in Systemic Lupus Erythematosus. *Arthritis & Rheumatisim* 2002;46(5):1228-1232.
- Petri, Nagibuddin, et al. Memantine in Systemic Lupus Erythematosus: A Randomized Double Blind Placebo Controlled Trial. *Semin Arthritis Rheum* 2011(pubmed)
- Provenzale, et al. Lupus Related Myelitis:serial MRI findings.*AJNR Am J Neuroradio* 1994;15:1911-1917
- Takunaga, Saito, et al. Efficacy of Rituximab (anti- CD20) for Refractory Systemic Lupus Erythematosus Involving The Central Nervous System. *Ann Rheum Dis* 2007;66:470-475.

- Toloza, et al. Systemic Lupus Erythematosus in Multiethnic US Cohort(LUMINA). Arthritis and Rheumatism 2004;50(12):3947-3957.
- Rhiannon J, Systemic Lupus Erythematosus involving the nervous system: presentation, pathogenesis, and management. Clin Rev Allergy Immunol.
- Salmaggi, et al. Spinal Cord Involvement and Systemic Lupus Erythematosus: Clinical and Magnetic Resonance Finding in 5 Patients. Clin Exp Rheumatol 1994;12:389-394.
- Syuto, Shimizu, et al. Association of antiphosphatidylserine/prothrombin antibodies with Neuropsychiatric Systemic Lupus Erythematosus. Clin Rheumatol. 2009 July; 28(7):841-845.



Systemic Lupus Erythematosus

Edited by Dr Hani Almoallim

ISBN 978-953-51-0266-3

Hard cover, 554 pages

Publisher InTech

Published online 21, March, 2012

Published in print edition March, 2012

This book provides a comprehensive overview of the basic and clinical sciences of Systemic Lupus Erythematosus. It is suitable for basic scientists looking for detailed coverage of their areas of interest. It describes how advances in molecular biology have increased our understanding of this disease. It is a valuable clinical resource for practicing clinicians from different disciplines including rheumatologists, rheumatology fellows and residents. This book provides convenient access to information you need about cytokines, genetics, Fas pathway, toll like receptors and atherogenesis in SLE. Animal models have been reviewed as well. How to avoid delay in SLE diagnosis and management, in addition to various clinical manifestations including pregnancy and SLE have all been explained thoroughly in this book.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Alkhotani Amal (2012). Approach to Patients with SLE Presenting with Neurological Findings, Systemic Lupus Erythematosus, Dr Hani Almoallim (Ed.), ISBN: 978-953-51-0266-3, InTech, Available from: <http://www.intechopen.com/books/systemic-lupus-erythematosus/approach-to-sle-patients-presenting-with-neurological-findings>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen